REMARKS

Applicants appreciate the thorough examination of the present application as evidenced by the non-final Office Action dated August 24, 2007 (hereinafter, the "Office Action"). Applicants are also grateful to Examiners Agnieszka Boesen and Stacey Chen for participating in a telephone interview on December 3, 2007 (hereinafter, the "interview") with Applicants' U.S. legal representative Shawna Cannon Lemon and Applicant's European representatives Dr. Martin Horner, Dr. Peter Foster and Dr. Ian Hardie.

As noted in the Interview Summary dated December 5, 2007 provided by the Examiner, the participants discussed the pending application, particularly Claim 1, and the enablement and obviousness rejections of record.

In view of the helpful and constructive dialog expressed during the interview resulting in the indication that the enablement rejection will be withdrawn, Applicants set forth herein remarks that support the nonobviousness of pending Claims 1, 3, 6-16, 25, 28, 31 and 32.

More specifically, Claims 1, 3, 6-16, 25, 28, 31 and 32 stand rejected under 35 U.S.C. §103(a) as being obvious in view of the combination of GB 2 045 828 A to Ostreicher et al. (hereinafter, "Ostreicher et al.") in view of WO 96/05846 to Nebe (hereinafter, "Nebe") as evidenced by Encyclopedia Britannica. *See* Office Action, page 3. However, a review of Ostreicher et al. reveals that this reference discusses the use of depth filters to remove sub-micron contaminants such as bacteria, viruses or pyrogens from contaminated liquids. These contaminants are not the same as, or even similar to prion agents, which are protein molecules. Accordingly, the submicron contaminants discussed in Ostreicher et al. would not be expected to simulate soluble prion protein in the presence of plasma proteins as provided by the present invention. Applicants respectfully submit that Nebe et al. fails to cure the deficiencies of Ostreicher et al.

Nebe et al. investigated a method of removing prion infectivity from an extract derived from thymus glands, with retention of prions by membrane ultra-filtration being the main focus of the study.

Aspects of the present invention relate to completely removing prion agents from **protein solutions**, specifically blood plasma products, to ensure that such products could not transmit a prion infection to patients, i.e., rendering the liquid non-infective with respect to prion protein infectivity. It should be noted that blood plasma is a clear solution of soluble

proteins, and therefore, it was prion that would be present in a soluble state that was of concern to the present inventors. For experimental purposes, prion infectivity must be added to the process being simulated. Such prion infectivity is normally obtained from brain tissue, as this is where infectivity is highest. However, because brain tissue contains matter that is insoluble in aqueous media, the present inventors **first clarified** the brain extract by high-speed centrifugation to remove the insoluble matter **before** the prion agent was added to the plasma protein solution to be studied.

In Nebe et al., brain tissue was also used as a source of prion infectivity, but in this case, the brain homogenate **was not clarified** before being added to the process at least where the starting material, thymus glands, contains both soluble and insoluble matter. Crude brain homogenate, with its mixture of soluble and insoluble matter, therefore represented a suitable material for "spiking" the process of Nebe et al. Before membrane ultra-filtration could be carried out, the experimental process suspension had to be clarified; otherwise, the ultra-filtration membrane would have been blocked by the insoluble matter present. The suspension was therefore clarified in Nebe et al. by filtration through a series of four pre-filters (i.e., nylon gauze, followed by membrane filters with pore sizes of 2.0 μm, 0.8 μm and 0.2 μm). This pre-filtration stage would be expected to remove insoluble brain matter down to 0.2μm. However, the pre-filtration employed by Nebe et al. would not be expected to remove soluble prion infectivity or prion infectivity that was associated with particles smaller than 0.2 μm. Thus, it is therefore not surprising to one of ordinary skill in the art that Nebe et al. found that prion infectivity of the order of 10^5 LD_{50}/mL **was not removed** by the pre-filtration stage. Accordingly, Nebe et al. subsequently examined the membrane ultra-filtration procedure.

Nebe et al. did find that the remaining infectivity was removed by ultra-filtration using an Amicon S1Y30 membrane, an ultra-filtration membrane that has a molecular pore size cut-off of 30, 000 daltons. Notably, 30 kDa is equivalent to a pore diameter of 0.02 μm. The membrane ultra-filtration step had to be repeated by Nebe et al. in order to obtain complete removal of prion infectivity.

Hence, Nebe et al. provides that considerable prion infectivity passes through a filter with a pore size of 0.2 μm and that double filtration to 0.02 μm (membrane ultra-filtration) is required to completely remove this material.

In contrast, the present inventors found that the prion agent could be removed using a depth filter with a nominal pore size 30x greater than the final pre-filter, which in Nebe et al. failed to remove 10^5 LD_{50}/ml of prion infectivity and 300x greater than the pore size of the ultra-filtration membrane required by Nebe et al. to obtain complete removal (with two passes required). The present inventors found that prions could be removed from plasma protein solutions with a single use depth-filter with a pore size of 6 μm to render the liquid non-infective with respect to prion protein infectivity as recited in Claim 1.

Applicants respectfully submit that one of ordinary skill in the art would not be motivated to combine the cited references where Ostreicher et al. does not address protein material such as prion agents, does not provide any indication that the process would be suitable for prion proteins and there is no reason as to why one of ordinary skill in the art would consider modifying the Nebe et al. process absent the teachings of the present invention. Although Nebe et al. does address prion agents, this reference essentially teaches away from the present invention by teaching that a filter having a greater pore size than the filter recited in the present claims is necessary and further teaching that multiple filtration passes are needed. As such, if even combined, the cited references do not provide the present invention.

Accordingly, Applicants respectfully submit that Claims 1, 3, 6-16, 25, 28 and 31 and 32 are patentable over the cited references, and Applicants respectfully request that the obviousness rejection of these claims be withdrawn.

CONCLUSION

For at least the reasons discussed above, Applicants respectfully submit that the application has been placed in condition for allowance, and Applicants respectfully request allowance of all the pending claims and issuance of this application.

If, in the opinion of the Examiner, a further telephone conference would expedite the examination of this matter, the Examiner is invited to call the undersigned attorney at (919) 854-1400.

Respectfully submitted,

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Betty Lou Rosser
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